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Contemporary (2009-2014) clinical outcomes after femoro-popliteal bypass surgery for chronic limb threatening ischaemia (CLTI) are inferior to those reported in the UK Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL) trial (1999-2004)

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Abstract

Introduction: Bypass surgery (BS) remains the "gold standard" revascularisation strategy in patients with chronic limb threatening ischaemia (CLTI) due to infra-inguinal disease. The BASIL-1 trial showed that in CLTI patients who survived for 2 years or more, BS resulted in better clinical outcomes. Despite this, there has been an increasing trend towards an endovascular first approach to infra-inguinal CLTI. Our aim was to investigate whether changes in practice have impacted upon the clinical outcomes of BS in our unit ten years after BASIL-1.

Methods: Data for patients who underwent femoro-popliteal (FP) BS in BASIL-1 (1999-2004) were retrieved from trial case record forms. The comparator contemporary series (CS) comprised all patients undergoing FP BS for CLTI in our unit between 2009-2014. Demographic and clinical outcome data on CS patients were collected from the prospectively collected hospital electronic notes. Anatomic patterns of disease in the BASIL-1 and CS cohorts were scored using Bollinger and GLASS. Statistical analysis was performed in SAS v9.4.

Results: There were 128 BASIL-1 and 50 CS patients. Baseline age, gender, affected limb, and diabetes prevalence were similar, as were days spent in hospital out to 12 months and length of follow-up. BASIL-1 patients were more likely to be current smokers (p=0.000) and had a higher creatinine (p=0.04). The 30-day morbidity and mortality were higher in BASIL-1 (45.3% vs 22%, p=0.004). There was no significant difference between BASIL-1 and CS with regard to run-off Bollinger (37.7 v 32.1, p=0.167) and IP GLASS (0 vs 0, p=0.390) scores, with both groups having a median of 2 run-off vessels. Amputation free survival (62% vs 28%, HR 1.86, 95%CI 1.18-2.93, p=0.007), limb salvage (85% vs 69%, HR 2.31, 95%CI 1.14-4.68, p=0.02), overall survival (69% vs 35%, HR 1.66, 95%CI 1.00-2.74, p=0.05) and Major Adverse Limb Events (67% vs 47%, HR 1.93, 95%CI 1.15-3.22, p=0.01) were all significantly better in BASIL-1.

Conclusion: Although 30-day mortality and morbidity were significantly lower, all of the examined longer-term clinical outcomes after FP BS were significantly worse in the CS group a decade on from BASIL-1. Further research in the form of prospective cohort studies (PCS) and randomized controlled trials (RCT) is urgently required to determine if the CS data reported here are generalizable to current vascular surgical practice and, if so, to determine the reasons for these unexpected outcomes.

Introduction

Chronic limb threatening ischaemia (CLTI) is the most severe form of peripheral arterial disease (PAD) and is characterized by ischemic rest pain and/or tissue loss/gangrene[1,2]. The worldwide incidence of CLTI is increasing due to ageing and the growing incidence of diabetes mellitus and chronic kidney disease[3,4]. Despite recent advances in medical therapies and endovascular, surgical and hybrid revascularisation technologies and techniques, CLTI patients remain at high risk of cardiovascular mortality and morbidity, and limb loss[5]. With regard to evidence-based revascularisation (EBR), the first UK NIHR HTA-funded Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL-1) trial remains the only published randomised controlled trial (RCT) to have compared a bypass surgery (BS) first with a plain balloon angioplasty (PBA) first approach to infra-inguinal revascularisation in CLTI[6]. BASIL-1 showed that in patients likely to live for more than two years, overall (OS) and amputation free survival (AFS) were better following randomization to BS than to PBA. Despite this 'level 1' evidence in favour of BS over PBA, there has been a world-wide trend towards an endovascular first approach to the treatment of femoro-popliteal (FP) disease in patients with CLTI. Those advocating such an approach point to lower peri-procedural morbidity and mortality, and further claim that current best endovascular treatment (BET) results in far superior outcomes than those reported in BASIL[7-9]. Although not evidence-based, in many vascular units around the world, BS is increasingly reserved for those patients who cannot have endovascular intervention or where such intervention has failed. Due to the lack of published contemporary series (CS) of BS for CLTI, the impact of such practice on outcomes following BS is unknown. The aim of the present study, therefore, is to compare clinical outcomes following FP BS in a CS (2009-2014) from a single UK academic vascular unit with those reported in the BASIL-1 trial operated a decade earlier (1999-2004).

Methods

The BASIL-1 trial randomised 452 patients presenting with CLTI due to infra-inguinal disease to either a BS-first or a PBA-first revascularisation strategy. The recruitment period was 1999 to 2004 and follow up ended on 1 July 2007[10]. For the present analysis, the BASIL-1 cohort comprised trial patients undergoing primary FP BS with any conduit. The CS cohort comprised patients undergoing primary FP BS for CLTI with any conduit in our unit between 2009 and 2014 and follow-up ended on 31 May 2017. Within the CS study period (2009-2014), 132 FP BS were performed in our unit. Of these, 72 BS were for claudication (IC) or popliteal aneurysm disease and so were excluded; as were four contralateral BS and six secondary BS performed for failed endovascular interventions within the previous 12 months. This left 50 patients in the CS cohort undergoing primary FP BS for CLTI compared with 128 BASIL-1 patients.

The BASIL-1 and CS cohorts were compared in terms of baseline factors, 30-day mortality and morbidity, length of hospital stay out to 12 months and amputation-free survival (AFS), limb salvage (LS), overall survival (OS), and freedom from re-intervention (FFR) and major adverse limb events (MALE). FFR was defined as the absence of subsequent re-vascularization or intervention for any post-operative complications. Minor amputations were excluded as they were considered a consequence of the clinical presentation. Major amputation was defined as amputation above the ankle joint. Minor amputation includes amputation of single or multiple digits, or trans-metatarsal amputation (no Chopart's or Lisfrank amputations were performed within the trial). MALE was defined as any ipsilateral limb intervention (excluding minor amputation) after initial intervention. Bollinger[11] and Global Vascular Guideline (GVG) GLASS grade and scores were used to quantify the pattern of anatomical disease prior to intervention.

GLASS score is a new anatomical staging system designed by an expert global panel as part of the Global Vascular Guidelines on Chronic Limb Threatening Ischaemia. GLASS is part of the Patient, Limb, Anatomy paradigm presented in the GVG. GLASS involves choosing the target artery pathway (TAP) for endovascular revascularisation from the origin of the SFA (common and deep femoral disease are considered part of "inflow" and considered corrected prior to more distal revascularisation) to the foot with the aim of establishing in-line flow. Disease severity in FP and IP segments are graded separately on features including length of disease, stenosis or occlusion and level of calcification. FP and IP grades are combined within a matrix to determine GLASS stage. GLASS stage is believed likely to correlate with endovascular immediate technical success rates and 12-

month limb-based patency (LBP) GLASS has been presented at the European Society of Vascular Surgery, Lyon (France) 2017, and Society of Vascular Surgery VAM in San Diego (2017) and Boston (2018). The concept is that GLASS will act as an aid to shared-decision making and stratification within trials comparing different form of revascularisation. We understand that the the GVG on CLTI are likely to be published in EJVES and JVS supplement in Q4 of 2108.

Ethical approval was granted for the BASIL trial (ISRCTN – 45398889), no ethical approval was required for the CS data collection as this is classed as audit of clinical outcomes.

Hazard ratios were used to detect statistically important differences in outcomes using 95% confidence intervals. Differences between the cohorts were compared using t-test, chi-squared and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis was performed using SAS v 9.4.

Results

Patient age, gender, and prevalence of diabetes were similar in both cohorts. BASIL patients were more likely to be current smokers, less likely to be on best medical therapy (BMT), and had a higher baseline creatinine (**Table 1**). Immediate technical success rate, as judged by the operating surgeon, was very high in both the BASIL-1 (126/128, 98%) and CS (50/50, 100%) cohorts. Minor amputation rates were equivalent between the two cohorts (23.4% vs 20%, p=0.6) suggesting equivalent burden of tissue loss. BASIL-1 trial patients had a non-significantly longer mean (SD) index admission when compared to the CS patients (23.2 [26.3] vs 15.6 [20.3] days, p = 0.7). However, difference in cumulative inpatient hospital days by 12 months had virtually disappeared (24.2 [26.4] versus 27.3 [26.8] days, p = 0.5). BASIL-1 patients suffered significantly higher overall combined peri-operative (30-day) mortality and morbidity (45% vs 22%; p = 0.004), including higher rates of wound infection (p=0.02). However, there was no significant difference in major adverse cardiac events (MACE) (8% vs 2%, p=0.1) (**Table 2**). With regard to long-term clinical outcomes, AFS (62% vs 28%, HR 1.86, 95% CI 1.18-2.93, p=0.007), LS (85% vs 69%, HR 2.31, 95% CI 1.14-4.68, p=0.02), OS (69% vs 35%, HR 1.66, 95% CI 1.00-2.74, p=0.05) and MALE (67% vs 47%, HR 1.93, 95% CI 1.15-3.22, p=0.01) were all significantly better in the BASIL-1 cohort (**Figures 1-4**). FFR (76% vs 60%, HR=1.70, 95% CI 0.88 – 3.27, p=0.1) was non-significantly better in BASIL-1 when compared to the CS cohort (**Figure 5**). In terms of anatomic burden of disease, there was no significant difference between BASIL-1 and CS with regard to run-off Bollinger score (37.7 vs 32.1, p=0.167) and IP GLASS (0 vs 0, p=0.390) grade, with both groups having a median of 2 run-off vessels. Nor was there any difference between total Bollinger score (63.1 vs 65.4, p=0.926). However, patients in the CS had a significantly higher FP GLASS score (3 vs 4, p=0.000) (**Table 3**).

Discussion

In the present study, although peri-operative (30-day) mortality and morbidity were significantly lower, long-term clinical outcomes following primary FP BS for CLTI in our unit between 2009 and 2014 were significantly worse than those reported in the BASIL-1 trial a decade earlier (1999-2004). Further research is required to determine if the CS data reported here are generalizable to current vascular surgical practice and, if so, to determine the reasons for these unexpected data. Possible causes include a loss of surgical skills as a result of the overall reduction in open vascular procedures and/or a tendency to reserve BS for patients considered unsuitable for endovascular intervention due the severity of their tissue loss and/or the extent and complexity of their underlying disease[12-15]. While loss of surgical skills is certainly possible, this does not appear to be supported by the observation that CS patients had lower overall 30-day mortality and morbidity as well as a trend towards a shorter index admission[16-19]. With regard to the clinical severity of disease, the proportion of patients with tissue loss was similar in the two cohorts. We were unable to determine the extent of tissue loss in the CS patients with same precision as was the case in BASIL-1. However, using rates of minor amputation as a surrogate, it would seem that the severity of tissue loss was broadly similar in both groups. With regard to anatomic complexity of disease, the Bollinger scoring and GLASS grade would suggest a similar disease burden. Importantly the run off scores were almost identical for both groups suggesting that the outflow for bypass surgery was equivalent. Post procedural surveillance may have been different between the two cohorts. Surveillance post bypass was not prescriptive in BASIL-1, its use was not recorded and re-intervention was largely clinically driven. In the CS only 15 patients were enrolled in formal ultrasound graft surveillance, none had formal haemodynamic surveillance. As such, it is possible that differences in post bypass care could contribute to the difference in clinical outcomes observed.

An important question is the degree to which our practice and the outcomes reported here can be generalized more widely to current vascular and endovascular practice within the UK and elsewhere. Like many units, despite a lack of evidence indicating that endovascular intervention offers a more clinically effective and cost-effective option for CLTI patients who could have a vein bypass, and growing evidence that failed endovascular intervention compromises outcomes following subsequent BS, we have increasingly employed an endovascular first approach to the management of CLTI. Thus, during the study period (2009-2014), almost five times more (n = 237) patients had a FP endovascular intervention for CLTI than had BS (n = 50). In the UK, virtually all CLTI patients are managed within the National Health Service (NHS), where care is provided free at the point of delivery to all UK

and European Union citizens, by salaried vascular surgeons and interventional radiologists. As such, the “turf battles” and re-imbursement issues seen elsewhere in the world are largely irrelevant to UK practice. Rather, the main reason for our endovascular preference is probably a reluctance to subject elderly and co-morbid patients to prolonged surgery and, linked to that, a belief that an endovascular approach is associated with less resource utilization in terms of operating theatre time and bed days in hospital. However, these beliefs are not supported by hard data and we have to accept that our current practice may not be maximizing long-term clinical outcomes for the greatest number of our CLTI patients.

Interestingly, in the UK, Heikkila et al.[20] have recently published 1-year outcomes following lower limb revascularisation using data from the national vascular registry (NVR), hospital episode statistics (HES), and the office of national statistics (ONS). The authors conclude that overall survival and amputation rates have significantly improved over a 10-year period. They suggest that one reason for the observed improvement may be centralization of services due to increased specialization in vascular surgery. These UK national data would seem to starkly contradict those reported here from a single UK academic vascular unit. However, it must however be noted that Heikkila and colleagues grouped together a wide range of surgical and endovascular procedures, studies patients with CLTI and intermittent claudication (IC), and that their follow-up was short. Unfortunately, at the present time, there are very few other published data with which we can compare our own long-term outcome data. Thus, most surgical and endovascular CLTI cohorts reported in the literature have limited follow-up and/or mix CLTI with IC and/or mix FP with infra-popliteal (IP) procedures which makes interpretation of the data extremely difficult [21-23].

In summary, therefore, there is a clear and urgent need to perform further RCTs to determine the pros and cons of a BET-first versus a BS-first revascularisation strategy in sub-groups of CLTI patients presenting with different degrees of tissue loss and anatomic complexities of disease. To this end, in the UK, NIHR HTA is funding the BASIL 2 [24] and BASIL 3 [25] to inform practice in IP disease and the impact of drug eluting technologies in the FP segment respectively. In the US, NIH have funded the BEST-CLI[26] trial. Together, these on-going trials will report contemporary clinical outcomes in several thousand patients undergoing BET and BS for CLTI and inform EBR decisions going forward.

Conclusion

Although 30-day mortality and morbidity were significantly lower, all of the examined longer-term clinical outcomes after FP BS were significantly worse in the CS group a decade on from BASIL-1.

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